

# Reduction by Hoe 140, the B<sub>2</sub> kinin receptor antagonist, of antigen-induced nasal blockage

C.E. Austin, J.C. Foreman & \*G.K. Scadding

Department of Pharmacology, University College London, Gower Street, London WC1E 6BT and \*The Royal National Throat, Nose and Ear Hospital, Gray's Inn Road, London WC1X 8DA

In subjects with allergic rhinitis to house-dust mite (HDM), antigen challenge produced a significant increase in nasal blockage but had no effect on nasal vascular permeability. The B<sub>2</sub> kinin receptor antagonist, [D-Arg<sup>0</sup>,Hyp<sup>1</sup>,Thi<sup>2</sup>,D-Tic<sup>3</sup>,Oic<sup>4</sup>]-bradykinin (Hoe 140), 200 µg administered by intranasal aerosol 2 min prior to challenge with HDM, 500 u significantly reduced nasal blockage induced by the antigen challenge. The data are compatible with a role for B<sub>2</sub> kinin receptors in the nasal response to challenge with antigen which is responsible for nasal blockage.

**Keywords:** Allergic rhinitis; bradykinin B<sub>2</sub> antagonist; acoustic rhinometry; allergen challenge; Hoe 140

**Introduction.** Kinins have been implicated in the pathophysiology of allergic rhinitis. Bradykinin and kallidin appear in the nasal secretions of patients with allergic rhinitis (Svensson *et al.*, 1990), and intranasally applied bradykinin causes symptoms of rhinitis, including an increase in nasal blockage and an increase in nasal vascular permeability (Proud *et al.*, 1988). [D-Arg<sup>0</sup>,Hyp<sup>1</sup>,Thi<sup>2</sup>,D-Tic<sup>3</sup>,Oic<sup>4</sup>]-bradykinin or Hoe 140 is a highly potent and long-acting bradykinin antagonist, effective in B<sub>2</sub> kinin receptor-containing preparations (Hock *et al.*, 1991). The increase in nasal airways resistance and vascular permeability in the human nasal airway induced by administration of exogenous bradykinin is inhibited by Hoe 140 (Austin & Foreman, 1994a).

The aim of this study was to investigate the effect of Hoe 140 on the nasal response to antigen challenge in subjects with allergy to house-dust mite (HDM), to determine whether kinin-mediated effects contribute to the pathology of allergic rhinitis.

**Methods** Fifteen subjects (19–70 year old) took part in the study. They were taking no medication at the time of, or in the 4 weeks prior to, the study. All had positive skin prick and nasal provocation tests to antigen from the house-dust mite, *Dermatophagoides pteronyssinus* (HDM). All subjects gave informed consent and the study was approved by the local Ethics Committee.

Minimum nasal cross-sectional area (A min) was determined by acoustic rhinometry as previously described (Austin & Foreman, 1994b).

Symptoms of nasal blockage, itching, sneezing and running were recorded on a 10 cm visual analogue scale (Aitken, 1969).

Vascular permeability was determined by measuring albumin in nasal lavage (Naclerio *et al.*, 1983), using a radial immunodiffusion assay (Behring Diagnostics, Milton Keynes, U.K.).

Compounds were delivered in a volume of 100 µl, by means of a nasal pump spray (Perfect-Valois, U.K., Ltd.). Both house-dust mite antigen (Allerayde, Nottingham, U.K.) and Hoe 140 (Bachem, Saffron Walden, Essex, U.K.) were dissolved in sterile saline (NaCl, 154 mM) at concentrations of 5000 u ml<sup>-1</sup> and 2 mg ml<sup>-1</sup> respectively.

Ten subjects were treated by intranasal aerosol in a single-blind, cross-over manner with: (a) saline (vehicle) or (b) Hoe 140, 200 µg. The dose of Hoe 140 was chosen on the basis of *in vitro* studies (Hock *et al.*, 1991). Two minutes after the treatment, aerosol nasal challenge with HDM, 500 u

was performed. Subjects were randomly allocated to either of the two treatments. The cross-over treatment was conducted one week later.

At each attendance, subjects were first given an intranasal aerosol of sterile saline, followed by symptoms score collection and A min determination every 5 min over a 15 min period. The mean of these measurements formed the baseline. Subjects were then given either treatment (a) or (b) and A min values and symptom scores were collected 10 min after challenge with HDM.

The mean of the A min values for the left and the right nostrils was calculated for each measurement taken. The decrease in A min was expressed as % change from the pre-challenge, baseline values, in order to normalize the data.

The symptom scores for pre-challenge saline treatment and after each antigen challenge were obtained by measuring the lines on the visual analogue scale for each symptom.

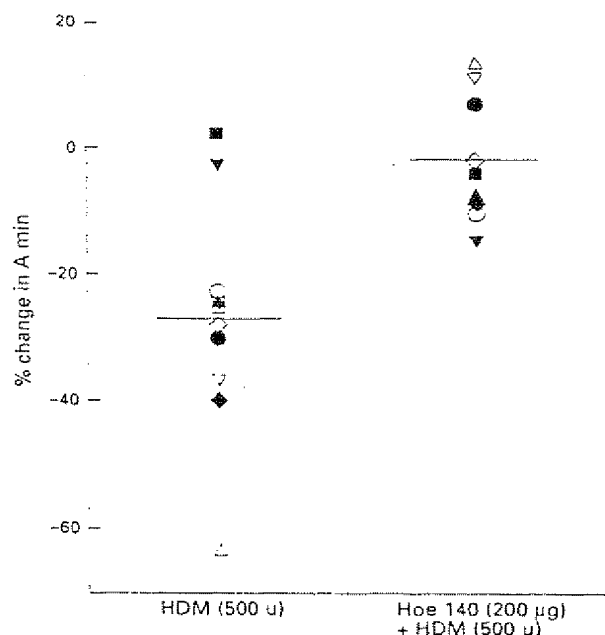
For albumin measurements, 5 different subjects participated in a single-blind, cross-over design similar to that described for acoustic reflection measurements, and the two treatment groups were the same. At each attendance, subjects were given an intranasal aerosol of sterile saline and nasal lavage was performed 10 min later. Subjects were then randomly allocated to treatments (a) or (b) and 10 min after challenge with HDM, 500 u nasal lavage was performed. One week later the cross-over experiment was performed. Albumin levels (g l<sup>-1</sup>) in the lavage were measured for the pre-challenge saline treatment and after the antigen challenges following treatment (a) or (b).

Data are presented as mean ± standard error of mean. Student's *t* test for paired data was used to evaluate statistically the differences between responses. A probability value of *P* < 0.05 is considered significant.

**Results** Intranasal administration of Hoe 140, 200 µg alone had no effect on A min (data not shown). Figure 1 shows that intranasal challenge with house-dust mite, 500 u, induced a decrease in A min of 27.2 ± 5.8% (*P* < 0.001, *n* = 10).

The symptom scores for saline control were: nasal blockage, 1.4 ± 0.7; running, 1.0 ± 0.8; itching, 1.1 ± 0.8 and sneezing, 0.4 ± 0.4. Following antigen challenge, the symptom scores increased to: nasal blockage, 4.2 ± 1.2; running, 1.5 ± 0.7; itching, 1.5 ± 1.1 and sneezing, 0.5 ± 0.3. Only the change in symptom score for nasal blockage induced by HDM was significantly different from the control score (*P* < 0.05).

Figure 1 shows that administration of Hoe 140, 200 µg prior to challenge with HDM, blocked the antigen-induced decrease in A min. The mean A min in the presence of



**Figure 1** The effect of the bradykinin antagonist, [D-Arg<sup>0</sup>,Hyp<sup>3</sup>, Thi<sup>1</sup>,D-Tic<sup>2</sup>,Oic<sup>5</sup>]-bradykinin (Hoe 140), 200 µg, given 2 min prior to challenge, on the response to intranasal challenge with house-dust mite, 500 u. The responses were measured 10 min after challenge and are expressed as % change from the baseline (saline) A min (minimal nasal cross sectional area) values which were  $0.4 \pm 0.1 \text{ cm}^2$  for the group challenged with house-dust mite and  $0.4 \pm 0.1 \text{ cm}^2$  for the group challenged with house-dust mite in the presence of antagonist, 200 µg. Each symbol represents a different individual. The horizontal bars represent the means from the 10 subjects.

Hoe 140 was significantly larger than the mean A min in the absence of Hoe 140 ( $P < 0.01$ ,  $n = 10$ ). In addition, Hoe 140 reduced symptom scores for: nasal blockage,  $1.1 \pm 0.7$ ; running,  $0.2 \pm 0.1$ ; itching,  $0.5 \pm 0.4$  and sneezing,  $0.4 \pm 0.3$ . The only significant reduction caused by Hoe 140 compared to antigen challenge alone was for nasal blockage ( $P < 0.05$ ).

Nasal challenge with HDM had no effect on the concentration of albumin measured in nasal lavage. Albumin levels after HDM were no different from control (saline) levels. The mean albumin concentration of nasal lavage prior to challenge with HDM was  $0.038 \pm 0.006 \text{ g l}^{-1}$  and after HDM challenge, it was  $0.029 \pm 0.008 \text{ g l}^{-1}$  ( $n = 5$ ,  $P < 0.05$ ).

**Discussion** We have shown that Hoe 140 reduces the effect of antigen challenge in causing nasal blockage in subjects with perennial allergic rhinitis to house-dust mite antigen. The magnitude of the effect of Hoe 140 at the dose we used was large and the data imply that the nasal blockage which

follows antigen challenge is mediated to a significant extent by kinin, formed in the nasal airway following antigen challenge.

Our data and those of others are consistent with the effect of bradykinin in the human nasal airway being mediated by a B<sub>2</sub> kinin receptor (Rajakulasingham *et al.*, 1991; Austin & Foreman, 1994a). Hoe 140 is a selective antagonist for B<sub>2</sub> receptors and so the fact that it inhibits antigen-induced nasal blockage indicates that a kinin is acting on a B<sub>2</sub> receptor to cause nasal blockage in perennial rhinitis to house-dust mite antigen. Although it is likely that Hoe 140 is acting at a B<sub>2</sub> receptor to inhibit the action of endogenous kinin generated by antigen challenge, we cannot exclude the possibility that Hoe 140 might reduce the formation of kinin, by inhibiting tissue kallikrein (Spragg *et al.*, 1988).

In contrast to our own data, we have recently learned that Hoe 140 does not block the symptoms of seasonal allergic rhinitis caused by exposure to pollen (Akbari & Bender, 1993). Interestingly, different types of rhinitis have been used as models in the two studies: perennial allergic rhinitis to house-dust mite and seasonal allergic rhinitis to pollens. Seasonal allergic rhinitis is characterized by sneezing, rhinorrhoea and nasal blockage, whereas the prominent feature of perennial allergic rhinitis is nasal blockage, with less marked rhinorrhoea and sneezing. The pathophysiology of the two types of allergic rhinitis may differ, with kinin being a major mediator of perennial but not seasonal rhinitis. Another reason for the difference in findings may be that the present study involved antigen provocation and objective measurement of responses in a laboratory, whilst the study of seasonal allergic rhinitis was based solely on symptom scores reported by patients during the pollen season.

Nasal blockage and an increase of nasal vascular permeability are detectable after aerosol administration of bradykinin (Proud *et al.*, 1988; Austin & Foreman, 1994a). However, in the present study, antigen provocation of subjects with perennial rhinitis to house-dust mite caused an increase in nasal blockage, but had no effect on nasal vascular permeability. We have previously shown that challenge of normal subjects with bradykinin causes nasal resistance and vascular permeability to increase, with similar dose-response curves and time-courses for the two effects (Austin & Foreman, 1994a). With antigen provocation, we have not detected increased vascular permeability. The antigen provocation may, in contrast to challenge with exogenous bradykinin, cause more local increases in kinins within the nasal airway, resulting in increased blood flow into nasal sinusoids, which may be more important in causing soft tissue swelling and nasal blockage than is swelling caused by plasma extravasation.

C.E.A. is an SERC CASE Scholar with Pfizer UK Ltd. as the industrial partners. We wish to express our gratitude to the subjects who took part in this study and to Mrs Yvonne Darby, at the Royal National Throat, Nose and Ear Hospital for her help with this study.

## References

- AITKEN, R.C.B. (1969). Measurement of feelings using visual analogue scales. *Proc. R. Soc. Med.*, **62**, 989-993.
- AKBARY, M.A. & BENDER, N. (1993). Efficacy and safety of Hoe 140 (a bradykinin antagonist) in patients with mild-to-moderate seasonal allergic rhinitis. In *Proceedings of Kinins 93*, Brazil, Abstract 22.02.
- AUSTIN, C.E. & FOREMAN, J.C. (1994a). A study of the action of bradykinin and bradykinin analogues in the human nasal airway. *J. Physiol.*, (in press).
- AUSTIN, C.E. & FOREMAN, J.C. (1994b). Acoustic rhinometry compared with posterior rhinomanometry in the measurement of histamine- and bradykinin-induced changes in nasal airway patency. *Br. J. Clin. Pharmacol.*, **37**, 33-37.
- HOCK, F.J., WIRTH, K., AUBUS, U., LINZ, W., GERHARDS, H.J., WILMER, G., HENKE, S.T., BREIPOHL, G., KÖNIG, W., KNOLLE, J. & SCHÖLKENS, B.A. (1991). Hoe 140 a new potent and long acting bradykinin-antagonist: *in vitro* studies. *Br. J. Pharmacol.*, **102**, 769-773.

- NACLERIO, R.M., MEIER, H.L., KAGEY-SOBOTKA, A., MEYERS, D., NOKMAN, P.S. & LICHTENSTEIN, L.M. (1983). Mediator release after nasal airway challenge with allergen. *Am. Rev. Respir. Dis.*, **128**, 597-602.
- PROUD, D., REYNOLDS, C.J., LACAPRA, S., KAGEY-SOBOTKA, A., LICHTENSTEIN, L.M. & NACLERIO, R.M. (1988). Nasal provocation with bradykinin induces symptoms of rhinitis and a sore throat. *Am. Rev. Respir. Dis.*, **137**, 613-616.
- RAJAKULASINGHAM, K., POLOSA, R., HOLGATE, S.T. & HOWARTH, P.H. (1991). Comparative nasal effects of bradykinin, kallidin and [Des-Arg<sup>7</sup>]-bradykinin in atopic rhinitic and normal volunteers. *J. Physiol.*, **437**, 577-587.
- SPRAGG, J., VAVREK, R.J. & STEWART, J.M. (1988). The inhibition of glandular kallikrein by peptide analog antagonists of bradykinin. *Peptides*, **9**, 203-206.
- SVENSSON, C., ANDERSSON, M., PERSSON, C.G.A., VENGE, P., ALKNER, U. & PIPKORN, U. (1990). Albumin, bradykinin and eosinophil cationic protein on the nasal mucosal surface in patients with hayfever during natural allergen exposure. *J. Allergy Clin. Immunol.*, **85**, 828-833.

(Received December 9, 1993)

Accepted January 17, 1994